

DOCKET NO.: CRDS-0062 (CRD0931CIP)

PATENT

Application No.: 10/829,074



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Robert Falotico, et al.

Confirmation No.: **5950**

Application No.: **10/829,074**

Group Art Unit: **3743**

Filing Date: **April 21, 2004**

Examiner: **Not yet assigned**

For: **Drug/Drug Delivery Systems for the Prevention and Treatment of Vascular Disease**

08/09/2006 HDESTA1 00000001 10829074

04 FC:1464 130.00 DP

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

**PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT
(37 CFR § 1.102 and MPEP § 708.02)**

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

Accompanying this petition is:

- a. A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement; and
- b. Supplemental Information Disclosure Statement.

2. Fee (37 CFR § 1.17(i))

The fee required is to be paid by:

☒ A check in the amount of **\$130.00** is attached.

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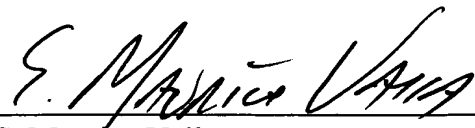
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- ☐ Please charge Deposit Account No. 23-3050 in the amount of **\$130.00**. This sheet is attached in duplicate.
- ☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

Date: August 7, 2006


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Registration No. 43,966

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Sir:

**DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE
SPECIAL BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)**

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. Claims 15 to 30 are presently pending. Each of the claims is directed to devices comprising an intraluminal stent, a nonerodible polymeric coating affixed to the stent, and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the coating; the devices provide an in-stent late loss in diameter at 12 months following implantation in a human of less than about 0.5 mm, as measured by quantitative coronary angiography. Claim 16 specifies an in-stent late loss in diameter of less than about 0.3 mm, and claims 17 and 18 specify that the stent provides an in-stent diameter stenosis at 12 months following implantation in a human of less than about 22% or 15%, respectively, as

measured by quantitative coronary angiography. Claims 19 to 22 are similar to claims 15 to 18, but specify mean in-stent late loss and in-stent diameter stenosis values for in a human population. Claims 23 to 30 are directed to methods of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty, comprising implanting in the lumen of said coronary artery a drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating. These methods provide in-stent late loss and/or in-stent diameter stenosis values as recited in claims 15 to 22.

2. Attached as exhibits hereto are press releases issued by Guidant Corporation (“Guidant”) describing certain of its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it has received Conformité Européene (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it “is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006.”

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant’s manufacturing facility for XIENCE™ V.

4. Since Guidant’s approved manufacturing facility for XIENCE™ V is in Temecula, California, I conclude that the “ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V” to which Guidant’s January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I conclude that Guidant is “making” XIENCE™ V and building inventory in the United States to support launch of the product in Europe.

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases and other publicly available documents, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 15 to 30 on file in this application.

7. Everolimus is a macrocyclic triene analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 5,6). An article published in EuroIntervention in 2005 (Exhibit 7) confirms that everolimus binds with FKBP12 (*see* page 59, col. 1), and that XIENCE™ V product comprises a stent bearing a coating that comprises a nonerodible polymer blended with everolimus (*see* page 59, col. 2). On the basis of this information, I conclude that the XIENCE™ V product comprises an intraluminal stent, a nonerodible polymeric coating affixed to the stent, and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the coating, as recited in claims 15 to 30 on file in this application.

8. Another article published in EuroIntervention in 2005 (Exhibit 8) reports on one-year results from Guidant's SPIRIT FIRST clinical trial, in which intravascular ultrasound and quantitative angiographic analyses were performed one year following intraluminal implantation of XIENCE™ V stents in the coronary arteries of human patients. The article reports that mean in-stent late loss and diameter stenosis values were 0.24mm and 18%, respectively (*see* abstract), which is within the limits recited in claims 15 to 30 on file in this application.

9. It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of claims 15 to 30 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

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10. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

☒ having been filed

☒ being filed

in a respective Information Disclosure Statement.

11. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: August 7, 2006



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Guidant Receives European Approval for Drug Eluting Coronary Stent

Company Achieves CE Mark Approval Ahead of Schedule; XIENCE V Launch Slated for Second Quarter

Indianapolis, Ind. and Brussels — January 30, 2006 — Guidant Corporation (NYSE: GDT) today announced that the company has received Conformité Européene (CE) Mark approval for the XIENCE™ V Everolimus Eluting Coronary Stent System. This regulatory certification allows Guidant to begin marketing the drug eluting stent in the 25 countries of the European Union. In addition, the CE Mark Approval is used to support market registrations in other regulated countries including those within Asia, Latin America and Eastern Europe.

"This early approval represents a significant milestone in Guidant's drug eluting stent program and demonstrates our ongoing commitment to advancing the field of cardiovascular therapy through innovative solutions," said John M. Capek, Ph.D., president, Vascular Intervention, Guidant. "The development of XIENCE V represents years of hard work and dedication by our employees and by trial investigators. We look forward to bringing this next-generation therapy to physicians and patients."

The XIENCE V Everolimus Eluting Coronary Stent System utilizes Guidant's most advanced coronary stent system, the highly deliverable cobalt chromium MULTI-LINK VISION®, which is available on the preferred rapid-exchange platform. Everolimus has been shown to reduce tissue proliferation in the coronary vessels following stent implantation.

"Completion of the CE Mark approval process for XIENCE V follows on the heels of impressive clinical results from the SPIRIT FIRST trial, which demonstrated the benefits of an everolimus drug eluting stent," said Prof. Patrick W. Serruys, M.D., of the Thoraxcenter, Erasmus University Hospital, Rotterdam, who served as the study's principal investigator. "With this approval, physicians in Europe will have an excellent treatment option for patients requiring a drug eluting stent."

Guidant is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE V beginning in the second quarter of 2006.

In November, Guidant announced completion of enrollment in only four months of SPIRIT II, a 300-patient, randomized clinical trial evaluating XIENCE V. The single-blind, prospective, randomized, non-inferiority study further evaluates the XIENCE V compared to the TAXUS® Express 2™ Paclitaxel-eluting coronary stent system for the treatment of coronary artery disease.

Guidant's 1,380-patient SPIRIT III global clinical trial is evaluating the XIENCE V Stent System in the United States and Japan. The randomized U.S. cohort, which will support U.S. Premarket Approval submission, has enrolled more than 70 percent of the required patients and is expected to complete enrollment later this quarter.

Guidant Corporation pioneers lifesaving technology, giving an opportunity for better life today to millions of cardiac and vascular patients worldwide. The company develops, manufactures and markets a broad array of products and services that enable less invasive care for some of life's most threatening medical conditions. For more information visit www.guidant.com.

This release includes forward-looking statements concerning XIENCE V. The statements are based on assumptions about many important factors, including satisfactory enrollment and completion of the clinical trial, associated regulatory processes and timelines, and other factors identified on Exhibit 99 to the company's most recent filing on Form 10-Q. Actual results may differ materially. The company does not undertake to update its forward-looking statements.

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Guidant Provides Update

Indianapolis, Ind. — October 19, 2005 — Guidant Corporation (NYSE: GDT), a world leader in the treatment of cardiac and vascular disease, today responded to statements by Johnson & Johnson on its pending acquisition of the Company and provided an update on its two major businesses.

Transaction Update

In response to Johnson & Johnson's comments yesterday, Ronald W. Dollens, president and CEO of Guidant Corporation, stated, "While neither company depends on this transaction for its continued future success, Guidant believes that the strategic rationale for combining the two companies is as strong today as when we entered into the Merger Agreement." Guidant anticipates that the pending transaction will receive FTC clearance in October. The Company does not expect to make any specific comments on the pending transaction until after FTC approval.

Business Performance

"Guidant's third quarter results will reflect the temporary unavailability of the CONTAK RENEWAL 3 and 4 family of heart failure devices during the full month of July and part of August, partially offset by sequential growth of U.S. coronary stent revenue, and continuing sales growth of our emerging businesses," Dollens reported. "At the end of the quarter, data suggest our implantable defibrillator implant rate exceeded 80 percent of the pre-product notification level and is over 100 percent of the rate one year ago."

Dollens continued, "As previously announced, Guidant is launching several recently approved cardiac rhythm management systems during the fourth quarter, including the revolutionary Latitude Patient Management system.

Physicians are expressing enthusiasm for the new wireless capability to monitor patients, improve their compliance, and monitor device status independent of patient effort." Dollens further observed, "Our drug eluting stent development program continues to make important progress toward European launch during the first half of next year. We are expanding manufacturing capacity, increasing productivity, and recently received FDA approval to expand clinical trial enrollment."

"While recent events and the publicity surrounding them will impact our short-term results, we believe that the fundamentals of our business and the markets that we serve remain strong and our outlook is positive," Dollens noted.

"Our track record of success over the years has been driven in large part by the dedication of our people to the needs of patients and physicians who use our products. We continue to be committed to providing the highest quality products for patients who critically need them and we are confident that the value of the Company remains strong."

Cardiac Rhythm Management Products Update

Consistent with an anticipated new product cycle, several significant new products were approved (cleared) by FDA during the third quarter. They include:

- VITALITY HE implantable defibrillator; Guidant's first high-energy product to offer the advanced functionality of the VITALITY family.
- CONTAK RENEWAL 3 RF cardiac resynchronization-defibrillator; this is Guidant's first wireless and wandless CRT-D and is designed to enhance the speed and convenience of patient care.
- ZOOM LATITUDE programmer; this next generation programmer is designed to interface with devices that include remote monitoring capability.

- LATITUDE Communicator and secure data storage system; these elements represent the final components of the Latitude Patient Management system.

Actions taken by the Company during the quarter reflect Guidant's commitment to provide more timely information to physicians and patients about our devices. Our products continue to demonstrate high performance and reliability, and tens of thousands of people are alive today and hundreds of thousands feel better as a result of Guidant's technologies. Guidant will continue to focus on meeting and exceeding the expectations of physicians, patients and the FDA.

Drug Eluting Stent Progress

Guidant announced today that its drug eluting stent development program continues to demonstrate progress and the Company has enrolled more than 500 patients in the SPIRIT II and III clinical trials since June. SPIRIT III is a large-scale pivotal clinical trial evaluating XIENCE™ V, an everolimus eluting coronary stent system utilizing Guidant's cobalt chromium rapid-exchange MULTI-LINK VISION® RX Coronary Stent System platform. Guidant plans to use the results of the SPIRIT III trial to obtain FDA approval for XIENCE V for the treatment of coronary artery disease. Results of the SPIRIT II study will provide additional clinical data to support the launch of XIENCE V in Europe and several countries outside the United States.

Earlier in the quarter, Guidant announced attainment of an enrollment milestone in the Company's exclusive license agreement with Novartis Pharma AG. Novartis supplies everolimus to Guidant for use in drug eluting stents and provides access to data supporting Guidant filings with regulatory agencies.

In addition, the Company plans to present one-year follow up data from SPIRIT I at the American Heart Association meeting in November 2005. SPIRIT I is a prospective, randomized, single-blind pilot study evaluating XIENCE V versus an uncoated MULTI-LINK VISION Coronary Stent System control in de novo (previously untreated) lesions.

During the quarter, the Company also announced that it successfully concluded an inspection of its drug eluting stent manufacturing and quality systems at its Temecula site. This inspection was conducted by Guidant's European Notified Body, which is also reviewing the Company's submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. The Notified Body found no nonconformities and will recommend certification for Guidant's manufacturing facility.

Guidant Corporation

Guidant Corporation pioneers lifesaving technology, giving an opportunity for a better life today to millions of cardiac and vascular patients worldwide. The Company, driven by a strong entrepreneurial culture of more than 12,000 employees, develops, manufactures and markets a broad array of products and services that enable less invasive care for some of life's most threatening medical conditions. For more information, visit www.guidant.com.

This release includes forward-looking statements that are based on assumptions about many important factors, including market trends and competition, particularly in connection with expanded indications and reimbursement for cardiac rhythm management products; satisfactory clinical and regulatory progress; progress with respect to the merger, including satisfaction of conditions to closing, including antitrust approvals; economic conditions, including exchange rates; litigation developments; and the factors listed on exhibit 99 to Guidant's most recent 10-Q. As such, they involve risks that could cause actual results to differ materially. The company does not undertake to update its forward-looking statements.

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ABBOTT COMPLETES ACQUISITION OF GUIDANT VASCULAR BUSINESS**—COMBINATION OF ABBOTT'S AND GUIDANT'S VASCULAR ORGANIZATIONS CREATES
LEADING VASCULAR DEVICES BUSINESS —**

Abbott Park, Illinois, April 21, 2006 — Abbott today announced it has completed the acquisition of Guidant's vascular business, which, combined with Abbott's current vascular business, creates one of the leading global vascular devices companies. This acquisition was made in connection with Boston Scientific's acquisition of Guidant Corporation.

"The acquisition of Guidant's vascular business builds on our broad-based business strategy to develop leading positions in attractive health care markets – shaping Abbott for greater balance and strengthening our business mix and breadth of pipeline opportunities," said Miles D. White, chairman and chief executive officer, Abbott.

"The combined Abbott and Guidant business offers a broad line of leading coronary and endovascular products, a pre-eminent sales force, and global manufacturing operations, as well as a state-of-the-art R&D organization, which is developing innovative technologies and devices such as the XIENCE™ V and ZoMaxx™ drug-eluting stents," White said. "Our newly expanded vascular organization has the tools and the talent to transform the way physicians treat vascular disease, impacting the lives of millions of patients around the world."

Broad Vascular Devices Product Portfolio

For the past several years, Abbott has built a competitive vascular business through acquisitions, licensing agreements, and internal scientific and commercial development. With the addition of Guidant's vascular business, Abbott offers physicians, catheterization labs and clinics a complete line of products and technologies for interventional procedures including: a comprehensive line of coronary and endovascular stents; a full offering of guide wires, catheters and balloons; and innovative vessel closure devices. In addition, the combined business has a broad portfolio of intellectual property, including rapid exchange technology and stent designs, enabling the company to operate effectively in the competitive vascular devices market.

Innovative Research and Development Programs

In addition to its broad product portfolio, Abbott is conducting advanced research and development programs that are focused on finding innovative solutions for treating vascular disease. With Guidant, Abbott now has two drug-eluting stents in development: ZoMaxx, a state-of-the-art stent coated with a proprietary immunosuppressant drug, zotarolimus, designed specifically to combat vessel re-narrowing; and XIENCE V, an everolimus-eluting stent on the MULTI-LINK VISION® cobalt chromium stent platform, which recently received approval in Europe. The combined organization also is leading the industry with a number of next-generation research programs including a stent that elutes two drugs targeted at difficult-to-treat patients such as diabetics, and a bioabsorbable drug-eluting coronary stent designed to be fully absorbed by the vascular tissue following the restoration of blood flow.

Guidant Vascular Sales and Employees

The transaction provides Abbott with Guidant's vascular intervention and endovascular solutions business units, which had combined sales of more than \$1 billion in 2005. These business units add nearly 6,000 employees worldwide to Abbott in three primary locations: Santa Clara, California; Temecula, California; and Clonmel, Ireland. The addition of Guidant's California-based employees boosts Abbott's presence in the state – currently the headquarters

of Abbott's diabetes care and vascular businesses – from more than 3,000 to more than 7,000 employees.

Financial Details

Abbott paid \$4.1 billion in cash for Guidant's vascular business. In addition, Abbott will pay Boston Scientific milestone payments of \$250 million at U.S. Food and Drug Administration approval of Guidant's drug-eluting stent, and an additional payment of \$250 million upon a similar approval in Japan. Abbott also provided Boston Scientific with a five-year, \$900 million interest-bearing loan. In addition, Abbott has purchased approximately 64 million shares of Boston Scientific stock for \$1.4 billion, which represents less than 5 percent of the company.

Abbott expects that the Guidant transaction will be accretive to earnings per share in 2007 and beyond. Further information, including financial details, will be provided on the conference call scheduled for 8 a.m. Central time today (9 a.m. Eastern), as previously announced. A live webcast of the conference call will be accessible through Abbott's Investor Relations Web site at www.abbottinvestor.com. An archived edition of the call will be available after 11 a.m. Central time. Abbott also furnished an 8-K today regarding the Guidant transaction.

About Abbott

Abbott is a global, broad-based health care company devoted to the discovery, development, manufacture and marketing of pharmaceuticals and medical products, including nutritionals, devices and diagnostics. The company now employs 65,000 people and markets its products in more than 130 countries.

**Private Securities Litigation Reform Act of 1995 —
A Caution Concerning Forward-Looking Statements**

Some statements in this news release may be forward-looking statements for the purposes of the Private Securities Litigation Reform Act of 1995. We caution that these forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those indicated. Economic, competitive, governmental, technological and other factors that may affect Abbott's operations are discussed in the "Risk Factors" section and Exhibit 99.1 of our Securities and Exchange Commission Form 10-K for the period ended December 31, 2005, and are incorporated by reference. We undertake no obligation to release publicly any revisions to forward-looking statements as the result of subsequent events or developments.

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Abbott's Vascular Business Fact Sheet

The combined Abbott and Guidant vascular business offers physicians, catheterization labs and clinics a complete line of products to treat patients with cardiac, vascular and biliary disease. Products and technologies for interventional procedures include: a comprehensive line of coronary and endovascular stents; a full offering of guide wires, catheters and balloons; and innovative vessel closure devices. Bolstered by the acquisition of Guidant's vascular business in April 2006, Abbott began building its vascular presence with the 1999 acquisition of Perclose, a pioneer in vessel closure technologies. Over the next few years, Abbott strategically assembled a comprehensive vascular devices business through a series of acquisitions, licensing agreements and internal development.

Abbott's Vascular Business – At a Glance

| | |
|-------------------------|---|
| Worldwide headquarters: | San Francisco Bay Area |
| Web address: | www.abbottvascular.com |
| Primary businesses: | Coronary, Endovascular and Vessel Closure Devices |
| Employees: | 8,000 (including nearly 6,000 from Guidant) |
| Facilities: | More than 10 commercial, R&D and manufacturing facilities worldwide |

Product Portfolio

Abbott offers comprehensive product lines throughout the world in three key areas of focus: coronary, endovascular and vessel closure devices. Key product lines and products include:

Coronary Products:

With Abbott's long history in health care and the advanced medical devices developed by Abbott Vascular and Guidant, the company is uniquely positioned to bring physicians and their patients innovative products for the treatment of coronary artery disease.

Drug-eluting Coronary Stents: The *Xience V* stent, approved for sale in Europe, is an everolimus-eluting stent utilizing the *Multi-Link Vision* cobalt chromium stent platform and Novartis' everolimus.

Bare Metal Coronary Stents: Comprehensive line of bare metal stents designed for a variety of vessel sizes and clinical situations (*Multi-Link Vision* family). The *TriMaxx* bare metal stent is available outside the United States.

Guide Wires: Full lines of coronary guide wires to assist the interventional cardiologist in accessing treatment area (*Hi-Torque* and *Asahi PTCA*).

Catheters: A variety of balloon dilatation catheters and specialty catheters designed to restore blood flow to stenosed arteries (*Tornus* specialty catheter; *Mercury* balloons and *Jogrophy* catheters; *Voyager*, *CrossSail*, *PowerSail* and *HighSail*).

Endovascular Products:

Abbott delivers an advanced portfolio of endovascular and biliary products to assist clinicians in a broad range of diagnostic and interventional procedures outside the coronary area (including carotid arteries, renal arteries and bile ducts).

Carotid Stents and Embolic Protection Devices: For the treatment of carotid artery disease. *RX Acculink* is an open-cell, self-expanding nitinol stent available on a rapid exchange delivery system. It is used in conjunction with *RX Accunet* embolic protection device, a polyurethane filter with a nitinol basket. *Xact* is a closed-cell, self-expanding stent used in conjunction with *Emboshield Embolic Protection System*, which features *Barewire*, a proprietary technology allowing for excellent stent placement.

Biliary stent systems: Broad lines of self-expanding and balloon expanding stents for a variety of applications (*RX Herculink*, *Omnalink* and *Jostent* balloon-expandable stent systems; and the *Absolute*, *Dynalink*, *Xceed* and *Xpert* self-expanding stent systems).

Peripheral Catheters and Guide wires: Full product lines of catheters and guide wires for various vessels and obstructions (*Agiltrac*, *Viatracs*, *Fox PTA*, and *Jocath* catheters; *Hi-Torque* guide wires).

Vessel Closure Products:

A pioneer in vessel closure technologies, Abbott offers products designed to facilitate faster, safer and more secure closure of the vascular access site following catheterizations.

Clip-based closure: The *StarClose Vascular Closure System* delivers a tiny circumferential flexible clip onto the surface of the femoral artery, mechanically closing the access site in the femoral artery securely in a matter of seconds following diagnostic catheterization procedures.

Suture-mediated closure: Minimally invasive vessel closure devices that utilize sutures and automate the surgical closure of femoral artery puncture sites following diagnostic or interventional procedures (*Perclose ProGlide*, *Perclose AT* and *Closer S*).

Leading Vascular R&D Program

In addition to its broad product portfolio, Abbott is conducting advanced research and development programs that are focused on finding innovative solutions for vascular disease.

Drug-eluting stents

Abbott has two drug-eluting stents in development: *Xience V* and *ZoMaxx*.

- The *Xience V* stent is an everolimus-eluting stent utilizing the *Multi-Link Vision* cobalt chromium stent platform and Novartis' everolimus. *Xience V* recently received regulatory approval in Europe and is expected to be launched in the third quarter of 2006. The product is also currently an investigational device in the United States and Japan.
- The *ZoMaxx* stent elutes zotarolimus, a proprietary immunosuppressant drug, and utilizes the *TriMaxx* stent platform, formed from a unique tri-layer composite that allows for thin struts while maintaining optimal visibility via X-ray. *ZoMaxx* is currently in clinical trials in both the United States and internationally, with an expected European launch in 2006.

The company also has a number of next-generation drug-eluting stent programs in development, including:

- A second-generation stent that elutes two drugs (zotarolimus and dexamethasone) intended for difficult-to-treat patients, such as diabetics, where restenosis rates are high.
- A bioabsorbable drug-eluting coronary stent designed to be fully absorbed by the vascular tissue following the restoration of blood flow.

Carotid stent clinical trials:

Abbott is a leader in studying carotid stenting as a minimally invasive alternative to surgery for patients with carotid artery disease, a leading cause of stroke. The company is sponsoring/participating in three clinical trials designed to investigate the benefits of carotid stenting in patients who are at risk of stroke from carotid artery disease.

- ACT I is the first company-sponsored clinical trial to compare carotid artery stenting to carotid artery surgery in asymptomatic patients who normally would be referred for surgery. ACT I utilizes Abbott's *Xact* stent and *Emboshield* embolic protection device.
- CAPTURE 2 is a 10,000-patient post-approval study of high-risk patients using the *RX Acculink* stent and *RX Accunet* embolic protection device.
- Abbott is also participating in the CREST study comparing carotid artery stenting to carotid surgery in normal-risk, symptomatic and asymptomatic patients who normally would be referred for surgery. CREST is sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institutes of Health (NIH). CREST utilizes the *RX Acculink* stent and *RX Accunet* embolic protection device.

###

* Trademarks are shown in italics in the text of this fact sheet.

1: Clin Pharmacokinet. 2004;43(2):83-95.

Clinical pharmacokinetics of everolimus.

Kirchner GI, Meier-Wiedenbach I, Manns MP.

Department of Gastroenterology, Hepatology and Endocrinology, Zentrum Innere Medizin, Medizinische Hochschule Hannover, Hannover, Germany.
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Everolimus is an immunosuppressive macrolide bearing a stable 2-hydroxyethyl chain substitution at position 40 on the sirolimus (rapamycin) structure. Everolimus, which has greater polarity than sirolimus, was developed in an attempt to improve the pharmacokinetic characteristics of sirolimus, particularly to increase its oral bioavailability. Everolimus has a mechanism of action similar to that of sirolimus. It blocks growth-driven transduction signals in the T-cell response to alloantigen and thus acts at a later stage than the calcineurin inhibitors ciclosporin and tacrolimus. Everolimus and ciclosporin show synergism in immunosuppression both in vitro and in vivo and therefore the drugs are intended to be given in combination after solid organ transplantation. The synergistic effect allows a dosage reduction that decreases adverse effects. For the quantification of the pharmacokinetics of everolimus, nine different assays using high performance liquid chromatography coupled to an electrospray mass spectrometer, and one enzyme-linked immunosorbent assay, have been developed. Oral everolimus is absorbed rapidly, and reaches peak concentration after 1.3-1.8 hours. Steady state is reached within 7 days, and steady-state peak and trough concentrations, and area under the concentration-time curve (AUC), are proportional to dosage. In adults, everolimus pharmacokinetic characteristics do not differ according to age, weight or sex, but bodyweight-adjusted dosages are necessary in children. The interindividual pharmacokinetic variability of everolimus can be explained by different activities of the drug efflux pump P-glycoprotein and of metabolism by cytochrome P450 (CYP) 3A4, 3A5 and 2C8. The critical role of the CYP3A4 system for everolimus biotransformation leads to drug-drug interactions with other drugs metabolised by this cytochrome system. In patients with hepatic impairment, the apparent clearance of everolimus is significantly lower than in healthy volunteers, and therefore the dosage of everolimus should be reduced by half in these patients. The advantage of everolimus seems to be its lower nephrotoxicity in comparison with the standard immunosuppressants ciclosporin and tacrolimus. Observed adverse effects with everolimus include hypertriglyceridaemia, hypercholesterolaemia, opportunistic infections, thrombocytopenia and leucocytopenia. Because of the variable oral bioavailability and narrow therapeutic index of everolimus, blood concentration monitoring seems to be important. The excellent correlation between steady-state trough concentration and AUC makes the former a simple and reliable index for monitoring everolimus exposure. The target trough concentration of everolimus should range between 3 and 15 microg/L in combination therapy with ciclosporin (trough concentration 100-300 microg/L) and prednisone.

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EXHIBIT 7

A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent: The SPIRIT first trial

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Conflict of interest: All authors declare no conflict of interest.

KEYWORDS

Stent, eluting stent, everolimus, randomized trial

Abstract

Background: Everolimus is a sirolimus analogue with similar efficacy in animal models, and has been previously successfully tested in humans using an erodable polymer.

Methods: This first-in-man single blind multi-centre randomized controlled trial assessed the safety and efficacy of everolimus eluting from a durable polymer on a cobalt chromium stent in patients with *de novo* native coronary artery lesions. Sixty patients were allocated to stent implantation with an everolimus-eluting stent (n=28) or an identical bare stent (n=32). Patients had either stable, unstable angina or silent ischaemia. Suitable lesions treated were single *de novo* native coronary lesions with 50-99% stenosis and could be covered by a 18 mm stent. The primary endpoint was in-stent late loss at 180 days, analysed on a per treatment basis. The major secondary endpoint was percent in-stent volume obstruction (%VO) as measured by intravascular ultrasound (IVUS) at 180 days. The clinical secondary endpoint was major adverse cardiac events (MACE) at 180 days.

Results: At 6 months, (matched pairs angiographic analysis), the in-stent late loss, percentage diameter stenosis and percentage of patients with binary restenosis were 0.10 mm, 16% and 0% respectively, in the everolimus arm (n=23), as compared with 0.87 mm, 39% and 25.9%, respectively in the bare stent arm (n=27, p<0.001 for late loss and diameter stenosis, p = 0.01 for restenosis). Significantly less neointimal hyperplasia was observed in the everolimus group compared to the bare stent group ($10 \pm 13 \text{ mm}^3$ vs $38 \pm 19 \text{ mm}^3$, p<0.001) and similarly, less volume obstruction ($8.0 \pm 10.4\%$ versus $28.1 \pm 14.0\%$, p<0.001). A major adverse cardiac event occurred in 2 patients in the everolimus arm versus 6 in the bare stent arm.

Conclusion: Everolimus eluted from a durable polymer on a cobalt chromium stent effectively suppresses neointimal growth at 6 months compared to an identical bare stent.

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Introduction

Recent studies that have evaluated the local application of anti-proliferative drugs (sirolimus and paclitaxel) for the prevention of restenosis via a stent delivery system have shown that these therapies successfully inhibit the development of neointimal hyperplasia^{1,2}.

Everolimus is an effective anti-proliferative agent³. On a molecular level, everolimus forms a complex with the cytoplasmic protein FKBP12. In the presence of everolimus, the growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1 is inhibited. The latter proteins are key proteins involved in the initiation of protein synthesis. Since phosphorylation of both p70 S6 kinase and 4E-BP1 is under the control of mammalian Target Of Rapamycin (mTOR), this finding suggests that, like sirolimus, the everolimus-FKBP12 complex binds to and thus interferes with its function. Disabling mTOR explains the cell cycle arrest at the late G1 stage caused by everolimus and sirolimus.

The feasibility of using everolimus on a drug eluting stent was determined by the FUTURE I trial⁴. This trial utilized an S-stent and bio-absorbable polymer system (both Biosensors International, Singapore) and confirmed the safety of the everolimus-eluting stent at 6 and 12 months. At 6 months, a 7.7% Major Adverse Cardiac Event (MACE) rate was observed with no thrombosis and no late incomplete apposition. The efficacy was demonstrated by significant reduction of in-stent tissue proliferation at 6 months: both angiographic in-stent late loss and IVUS% neointimal volume were reduced by 87%. No angiographic in-stent binary restenosis was observed in the everolimus-eluting stent arm. The 12 month FUTURE I results showed sustained safety and efficacy with no new MACE events, no aneurysms, no late stent malapposition, and no thrombosis observed between 6 and 12 months. Minimal Lumen Area and Luminal Volume Index were maintained up to 12 months and no in-stent binary restenosis was observed up to 12 months.

The SPIRIT First clinical trial represents the first clinical evaluation of the Guidant XIENCE™ V Everolimus Eluting Coronary Stent System (XIENCE™ V Everolimus Eluting CSS), to investigate the potential benefits of the local application of everolimus in a durable polymer in combination with a thin strut cobalt chromium stent.

Methods

Patient selection

This randomized single-blind trial was performed at 9 medical centers and enrolled patients from December 2003 to April 2004. It was approved by the ethics committee at each participating Institution, and all patients gave written informed consent.

Patients were eligible for the study if they were aged above 18 years and had received a diagnosis of stable or unstable angina or silent Ischaemia. Additional eligibility criteria were the presence of a single primary *de novo* coronary lesion that was 3.0 mm in diameter as assessed by on-line QCA, that could be covered by an 18 mm stent, a stenosis of between 50-99% of the luminal diameter, and a Thrombolysis In Myocardial Infarction (TIMI) flow grade of 1 or more. Patients were not eligible for enrollment if they had an evolving myocardial infarction, stenosis of an unprotected left main coro-

nary artery, an ostial location, located within 2 mm of a bifurcation, a lesion with moderate to heavy calcification, an angiographically visible thrombus within the target lesion, a left ventricular ejection fraction of less than 30%, were awaiting a heart transplant, or had a known hypersensitivity or contraindication to aspirin, heparin, clopidogrel, cobalt, chromium, nickel, tungsten, everolimus, acrylic and fluoro polymers or contrast sensitivity that could not be adequately pre-medicated.

The Everolimus-eluting stent

The Guidant XIENCE™ V Everolimus Eluting CSS is comprised of the Guidant MULTI-LINK VISION® Stent and delivery system, and a drug eluting coating. The Guidant MULTI-LINK VISION® Stent is a balloon expandable stent, which consists of serpentine rings connected by links fabricated from a single piece of medical grade L-605 cobalt chromium alloy.

Everolimus is blended in a nonerodable polymer (this drug layer was coated over another nonerodable polymer primer layer). This coating includes of acrylic and fluoro polymers, both approved for use in blood contacting applications. This layer of everolimus-polymer matrix with a thickness of 5-6 microns is applied to the surface of the stent and is loaded with 100 micrograms of everolimus per square centimeter of stent surface area with no top coat polymer layer. The stent is designed to release approximately 70% of the drug within 30 days after implantation.

Everolimus (Certican®, Novartis Corporation) has been evaluated in clinical trials in the US and Europe for use as an immunosuppressant following cardiac and renal transplantation⁵. Everolimus has received market approval in the European Union.

Study procedure

Following the confirmation of angiographic inclusion and exclusion criteria and prior to the procedure, patients were allocated through a telephone randomization service and assigned in a 1:1 ratio to either an everolimus eluting stent or bare metal stent. A single stent 3.0 mm in diameter, 18 mm long was used in the study.

Lesions were treated using standard interventional techniques with mandatory pre-dilatation and stent implantation at a pressure not exceeding the rated burst pressure. Due to packaging differences, physicians were not blinded to the device. Post-dilatation was allowed with a balloon shorter than the implanted stent. In the event of a dissection occurring at the edge of the implanted stent, it was recommended that a single additional bare Guidant MULTI-LINK VISION® stent be implanted as animal data only on single everolimus stent implantation were available at the onset of the study; these patients were *a priori* excluded from the per-treatment analysis but are part of the acute success population. IVUS was performed after angiographically optimal stent placement had been obtained and was repeated if additional post-dilatation was performed.

Intravenous boluses of heparin were administered according to local standard practice. Treatment with aspirin, at a minimum dose of 80 mg per day, was started at least 24 hours before the procedure and continued indefinitely. A loading dose of 300 mg of clopidogrel was administered 24 hours before the procedure, followed

by 75 mg daily for three months. Treatment with ticlopidine was permitted in case of clopidogrel hypersensitivity. Device success was defined as a final in-stent diameter stenosis of less than 50 percent by QCA using the assigned device. Clinical success was defined as the successful implantation of any device, with stenosis of less than 50 percent of the vessel diameter by QCA and no major cardiac events during the hospital stay.

Follow-up

Patients were evaluated at 30 days and 6 months. Further evaluations will be performed at 9 months and 1 year, with annual evaluations out to 5 years. At outpatient visits, patients were asked specific questions about the interim development of angina according to the Canadian Cardiovascular Society classification of stable angina. They were also monitored for MACE. Angiographic and IVUS evaluations were performed at 6 months, and will be repeated at 1 year. Prior to performing a follow-up angiogram, the physician was required to record in the source documents whether a revascularization (if required) was clinically indicated – defined as the presence of ischaemic symptoms and/or a positive functional ischaemia study.

Quantitative coronary angiography evaluation

Quantitative coronary angiography was performed using the CAAS II analysis system (Pie Medical BV, Maastricht, Netherlands). In each patient, the stented segment and the peri-stent segments (defined by a length of 5 mm proximal and distal to the stent edge) were analyzed. The following QCA parameters were computed: computer-defined Minimal Luminal Diameter (MLD), reference diameter obtained by an interpolated method, and percentage diameter stenosis. Binary restenosis was defined in every segment as diameter stenosis $\geq 50\%$ at follow-up. Late loss was defined as the difference between MLD post-procedure and MLD at follow-up. Results are presented as matched pairs in the manuscript and as unmatched pairs in the Appendix. Unmatched pairs data is most commonly presented and utilises the mean QCA results of all projections obtained. Matched pairs data is more accurate as it compares the same views post-procedure and at follow-up and uses only QCA data of identical projections.

Intravascular ultrasound analysis

Post-procedure and follow-up stented vessel segments were examined with mechanical or phased array Intravascular ultrasound using automated pullback at 0.5 mm per second. The coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was examined. A computer-based contour detection program was used for automated 3-D reconstruction of the stented and adjacent segments. The lumen, stent boundaries and external elastic membrane (vessel boundaries) were detected using a minimum cost algorithm. The Stent Volume (SV) and Lumen Volume (LV) were calculated according to Simpson's rule. The intra-stent neointimal volume was calculated as the difference between SV and LV. The percentage obstruction of the stent volume was calculated as intra-stent neointimal volume/stent volume $\times 100$. Feasibility, reproducibility and inter- and intra-observer variability of

this system have been validated *in vitro* and *in vivo*⁶. Incomplete apposition was defined as one or more stent struts separated from the vessel wall with evidence of blood speckles behind the strut on ultrasound, while late incomplete apposition was defined as incomplete apposition of the stent at follow-up which was not present post-procedure.

Study endpoints

The primary angiographic endpoint was In-stent luminal late loss, as determined by quantitative angiography. Secondary endpoints (QCA and IVUS) at 6 months and 1 year Included the in-stent and in-segment late loss, angiographic binary restenosis rate, percentage diameter stenosis; and In-stent percentage volume obstruction. In-stent was defined as within the margins of the stent while in-segment was defined as located either within the margins of the stent or 5 mm proximal or distal to the stent. Late loss was calculated as the difference between the follow-up and post-procedure minimum luminal diameter. Secondary clinical endpoints were a composite of major cardiac events, including cardiac death, Q-wave or non-Q-wave myocardial infarction, clinically driven surgical or percutaneous revascularization of the target lesion (MACE) or vessel (Target Vessel Failure) at 30 days, 6 months, 9 months, and annually up to 5 years after the index procedure; and acute device, procedure and clinical success. All deaths that could not be clearly attributed to another cause were considered cardiac deaths. A non-Q-wave myocardial infarction was defined by an increase in the creatine kinase level to more than twice the upper limit of the normal range, accompanied by an increased level of creatine kinase-MB, in the absence of new Q waves on electrocardiography.

The endpoints were adjudicated by an independent clinical events committee. In addition, a data and safety monitoring board that was not affiliated with the study sponsor reviewed the data to identify any safety issues related to the conduct of the study.

Statistical analysis

The primary endpoint and all trial endpoints were analyzed on the per-treatment evaluable population which consisted of patients who had no bailout stenting and no major protocol deviations, as evaluated in a blinded manner. Acute success was analyzed on the entire patient population.

The sample size for the study was determined based on the primary endpoint of in-stent late loss at 180 days and on the following assumptions: a single comparison of active to uncoated; one-tailed t-test, unequal and unknown variances in the two groups being compared; $\alpha=0.05$; true mean difference between the bare stent group and the treatment group of 0.48 mm. This assumption was made based on the results of the VISION Registry (mean late loss=0.83 mm)⁷, SIRIUS trial (mean late loss=0.17 mm)⁸ and TAXUS IV trial (mean late loss=0.39 mm)⁹. (Assume the true mean late loss for the treatment group is 0.35 mm, the difference between the bare stent group and treatment group is calculated as: 0.83 mm - 0.35 mm = 0.48 mm). The standard deviation was assumed to be 0.56 mm in the bare stent group and 0.38 mm in the treatment group (based on the results of the VISION Registry study and SIRIUS trial); approximately 20% rate of lost to follow-up or dropout; approximate-

ly 10% of patients with bailout stents. Given the above assumptions, 30 patients per arm (with the analysis of 22 evaluable patients per arm) will provide 95% power for comparison. Although the trial was not powered based on the major secondary endpoint, percent volume obstruction at 180 days, enrolling 30 patients per arm (analysis of 22 patients per arm) would provide more than 96% power.

Binary variables were compared using Fisher's Exact test. For continuous variables, means and standard deviations were calculated and groups compared using the Wilcoxon Rank-Sum test, except for the primary endpoint which was evaluated with a one sided *t*-test. Final 6-month results are presented in the manuscript, while the Appendix contains results that were available at the time that the 180-day report was prepared.

Results

Patient characteristics

Between December 2003 and April 2004, 28 patients were randomly assigned to receive the everolimus-eluting stent, and 32 were assigned to receive the bare stent. As defined in the protocol, all results (except acute success) are presented for the per-treatment population (27 patients in the everolimus group, and 29 patients in the bare stent group, Figure 1). In the everolimus group there was one bailout procedure, and in the bare stent group there were two bailout procedures and one major protocol deviation (the patient was on the heart transplant waiting list). With the exception of a significantly higher number of patients with hypertension requiring treatment in the everolimus group, the two groups were similar with respect to clinical variables examined (Table 1).

Table 1. Baseline characteristics of the per-treatment patient population and of each treatment group.*

| | Everolimus stent (n = 27) | Bare stent (n = 29) | All patients (n = 56) |
|---|------------------------------|------------------------|--------------------------|
| Age(yrs) | 64 ± 10 | 61 ± 9 | 63 ± 9 |
| Male gender (%) | 70 | 76 | 73 |
| Current smokers (%) | 28 | 31 | 30 |
| Diabetes (%) | 11 | 10 | 11 |
| Hypertension requiring medication (%) | 70 | 41 | 55 |
| Hyperlipidemia requiring medication (%) | 70 | 76 | 73 |
| Prior intervention (%) | 19 | 7 | 13 |
| Prior MI (%) | 24 | 14 | 19 |
| Stable angina (%) | 78 | 79 | 79 |
| Unstable angina (%) | 19 | 14 | 16 |
| Target vessel (%) | | | |
| Left anterior descending | 48 | 45 | 46 |
| Left circumflex | 22 | 21 | 21 |
| RCA | 30 | 34 | 32 |
| AHA / ACC Lesion Class (%)** | | | |
| A | 0 | 10 | 5 |
| B1 | 41 | 28 | 34 |
| B2 | 59 | 62 | 61 |
| C | 0 | 0 | 0 |
| Reference Vessel Diameter (mm ± SD) | 2.61 ± 0.40 | 2.71 ± 0.28 | 2.66 ± 0.34 |
| Lesion length (mm ± SD) | 10.1 ± 2.6 | 10.9 ± 3.3 | 10.5 ± 3.0 |

* There were no significant differences between the treatment groups except for Hypertension Requiring Medication (P=0.04)

** AHA / ACC = American Heart Association / American College of Cardiology

FIGURE 1

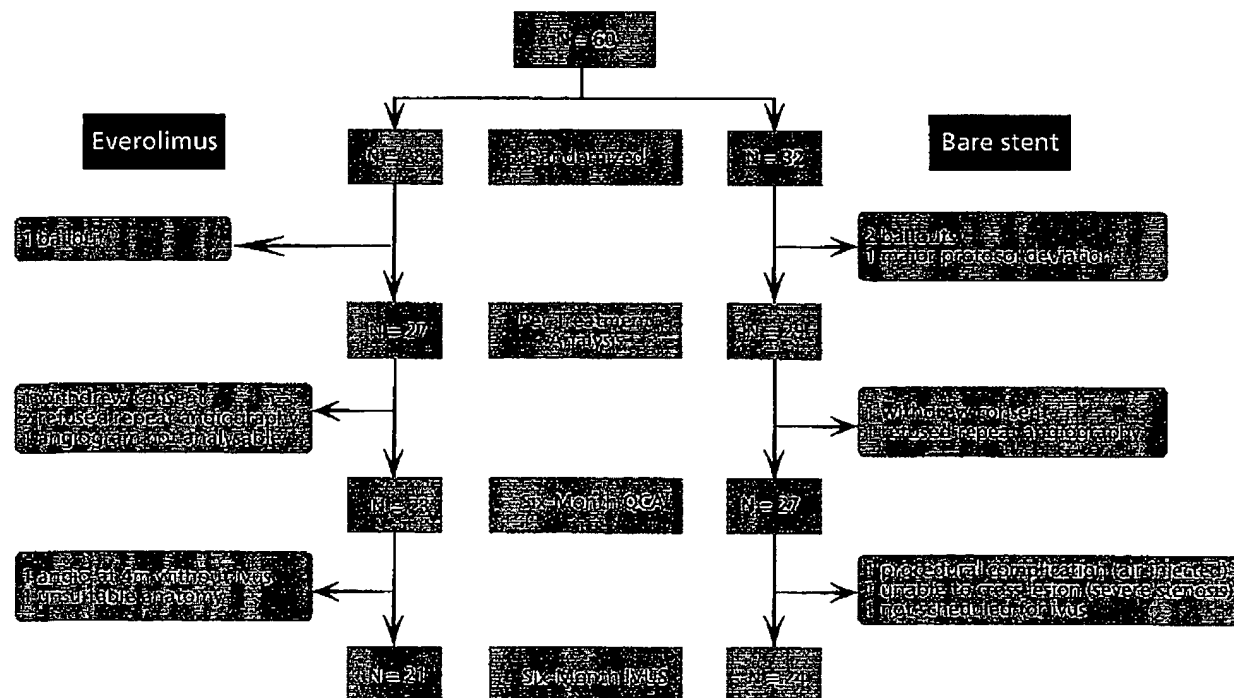


Fig. 1: Flowchart of patients

Procedural characteristics

The lesions in the two groups were treated similarly with the use of conventional techniques. Glycoprotein IIb/IIIa inhibitors, used at the investigators' discretion, were administered to 7.4% of the patients in the everolimus group and 3.4% of those in the bare stent group. The two groups did not differ significantly with respect to the rate of device success (96.4% in the everolimus group and 93.8% in the bare stent group) or clinical success (96.4% in the everolimus group and 100% in the bare stent group).

Quantitative coronary angiography analysis

Angiographic data at 6 months were available for 50 of the 56 analysable patients (89.3%). The mean reference diameter of the target vessel, the mean length of the lesion at baseline, the reference vessel diameter and mean MLD of the stented segment were similar in the two groups (Tables 1 and 2). At six months, with matched pairs analysis, the mean MLD of the stented segment was significantly greater in the everolimus group. The mean in-stent late loss, percentage of stenosis, and percentage of patients with 50 percent or more stenosis were 0.10 mm, 16%, and 0%, respectively, in the everolimus group, as compared with 0.87 mm, 39%, and 25.9%, respectively, in the bare stent group ($p < 0.001$ for late loss and diameter stenosis, $p = 0.01$ for restenosis). Figure 2 shows the cumulative frequency of stenosis immediately after the index procedure and at six months in each treatment group. Table 2 and Figure 3 show the results of sub-segmental quantitative angiographic analyses for matched pairs. The late luminal loss at both the proximal and the distal edges of the stent was less in the everolimus group than in the bare stent group ($p < 0.01$ for proximal and $p = 0.04$ for distal). The late luminal loss in the stented segment was significantly less in the everolimus group than in the bare stent group ($p \leq 0.001$).

Intravascular ultrasound evaluation

At six months follow-up, intravascular ultrasound evaluation showed no significant differences between the two groups with respect to the volume of the stent or the vessel volume (Table 3). Significantly

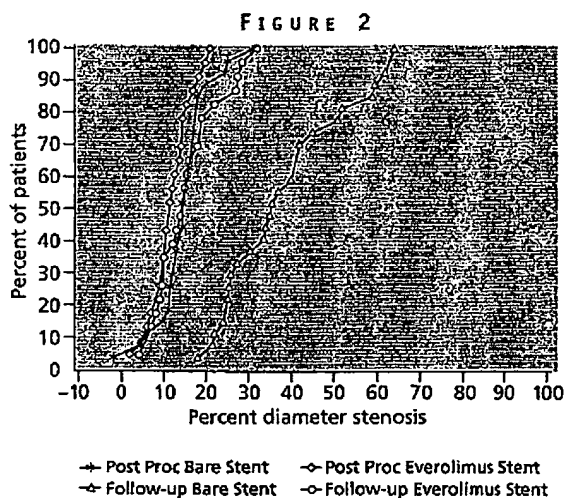


Fig. 2: Cumulative frequency of stenosis (in-stent) immediately after stenting and at six months

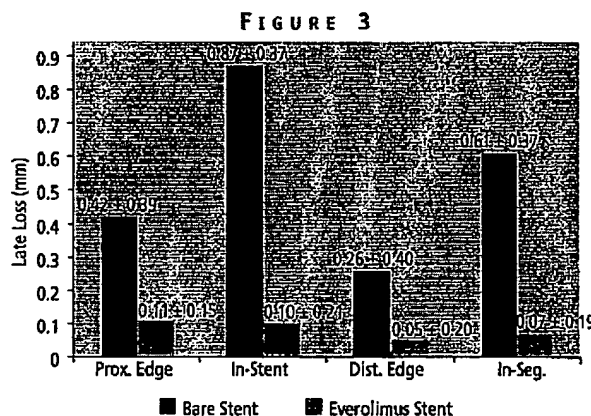


Fig. 3: Comparison of in-segment / in-stent late loss

Table 2. Results of sub-segmental quantitative coronary angiographic analysis (Matched Pairs).

| | Proximal edge | | | In-stent | | | Distal edge | | | In-segment analysis | | |
|---------------------------------------|-----------------------|----------------|---------|-----------------------|----------------|------------|-----------------------|----------------|---------|-----------------------|----------------|----------|
| | Everolimus- (n=23) | Bare (n=27) | P-value | Everolimus- (n=23) | Bare (n=27) | P-value | Everolimus- (n=23) | Bare (n=27) | P-value | Everolimus- (n=23) | Bare (n=27) | P-value |
| Reference Vessel Diameter (mm) | | | | | | | | | | | | |
| After procedure | 2.80 ± 0.33 | 3.04 ± 0.38 | 0.06* | 2.71 ± 0.28 | 2.89 ± 0.35 | 0.11* | 2.64 ± 0.30 | 2.80 ± 0.39 | 0.21* | 2.65 ± 0.30 | 2.84 ± 0.41 | 0.10* |
| At 6 months | 2.78 ± 0.32 | 2.67 ± 0.40 | 0.22* | 2.70 ± 0.31 | 2.58 ± 0.37 | 0.25* | 2.61 ± 0.37 | 2.46 ± 0.36 | 0.19* | 2.61 ± 0.36 | 2.59 ± 0.36 | 0.89* |
| Minimal Luminal Diameter (mm) | | | | | | | | | | | | |
| After procedure | 2.56 ± 0.44 | 2.61 ± 0.45 | 0.79* | 2.38 ± 0.25 | 2.45 ± 0.31 | 0.50* | 2.23 ± 0.41 | 2.26 ± 0.45 | 0.77* | 2.11 ± 0.35 | 2.14 ± 0.40 | 1.00* |
| At 6 months | 2.45 ± 0.46 | 2.19 ± 0.49 | 0.04* | 2.28 ± 0.33 | 1.58 ± 0.41 | < 0.001* | 2.18 ± 0.38 | 2.00 ± 0.45 | 0.21* | 2.04 ± 0.40 | 1.54 ± 0.41 | < 0.001* |
| Late Loss (mm) | 0.11 ± 0.15 | 0.42 ± 0.39 | < 0.01* | 0.10 ± 0.21 | 0.87 ± 0.37 | < 0.001*** | 0.05 ± 0.20 | 0.26 ± 0.40 | 0.04* | 0.07 ± 0.19 | 0.61 ± 0.37 | < 0.001* |
| Diameter Stenosis (%DS) | | | | | | | | | | | | |
| After procedure | 9 ± 11 | 14 ± 9 | 0.07* | 12 ± 5 | 15 ± 6 | 0.05* | 16 ± 10 | 20 ± 10 | 0.16* | 20 ± 8 | 24 ± 9 | 0.05* |
| At 6 months | 12 ± 12 | 17 ± 17 | 0.26* | 16 ± 8 | 39 ± 14 | < 0.001* | 16 ± 10 | 19 ± 14 | 0.82* | 22 ± 11 | 41 ± 14 | < 0.001* |
| Binary Restenosis Rates | 4.3% | 3.7% | 1.00** | 0.0% | 25.9% | 0.01** | 0.0% | 7.4% | 0.49** | 4.3% | 33.3% | 0.01** |

* two-sided Wilcoxon rank sum test ** two-sided Fisher's Exact test *** One-sided t-test † Fisher's Exact test

Table 3. IVUS measurements at 6 month follow-up.

| | Everolimus (n=24) | Bare (n=24) | p-value |
|---|----------------------|----------------|---------|
| Vessel volume (mm ³) | 291 ± 82 | 296 ± 73 | 0.64 |
| Stent volume (mm ³) | 134 ± 28 | 139 ± 33 | 0.69 |
| In-stent neo-intimal volume (mm ³) | 10 ± 13 | 38 ± 19 | <0.001 |
| Luminal volume (mm ³) | 124 ± 32 | 100 ± 31 | 0.04 |
| In-stent volume obstruction (%)** | 8.0 ± 10.4 | 28.1 ± 14.0 | <0.001 |

* This final table contains an additional 13 patients not included in the 180-day report prepared for the sponsor. In 8 patients (4 in each group), an imputed stent length of 18mm was used due to non-continuous pullback. In a further 5 patients (all bare stent group) results were unavailable at the time of the 180-day report. (see Appendix)

** In-stent volume obstruction = 100*
(In-stent neo-intimal volume / Stent volume)

less neointimal hyperplasia was observed in the everolimus-stent group compared to the bare-stent group (10 ± 13 vs. 38 ± 19 mm³, $p<0.001$) and similarly, significantly less volume obstruction, ($8.0 \pm 10.4\%$ versus $28.1 \pm 14.0\%$, $p<0.001$). Figure 4 is a cumulative curve of percentage volume obstruction. No in-stent volume obstruction was detected in almost half of the patients in the everolimus-stent group, whereas in the bare stent group, some degree of obstruction by neointima was present in all patients (Figure 4). No evidence of an "edge effect," aneurysm formation, in-stent thrombosis, persistent dissection or late incomplete apposition were observed.

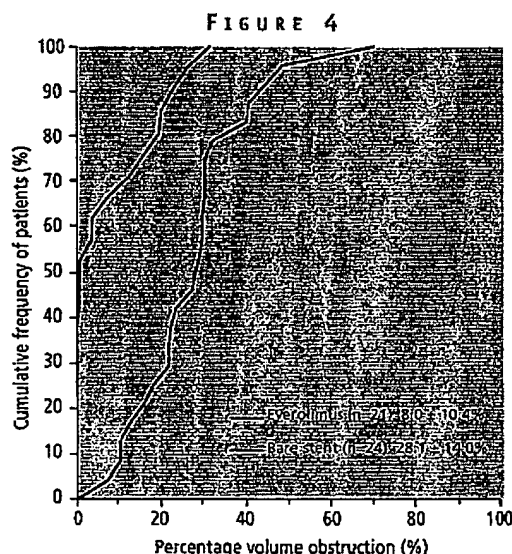


Fig. 4: Percentage in-stent volume obstruction versus cumulative frequency of patients. Values are expressed as mean ± standard deviation for each group.

Major adverse cardiac events

Major adverse cardiac events are listed in Table 4. There was one Q-wave myocardial infarction in the everolimus group in a patient who underwent additional revascularization for angina in a non-target vessel 18 days after the study procedure and suffered thrombosis of this non-study stent 12 days later. The everolimus stent was patent with no evidence of thrombus at the time of the thrombotic occlusion of the non study stent. One patient in the everolimus arm underwent a clinically driven target lesion revascularization at 3 weeks for symptomatic persistent dissection at the proximal edge left untreated at the time of the procedure. There were no clinically driven target revascularizations in the everolimus group for restenosis. There were six clinically driven target lesion revascularizations in the bare stent group, five were treated percutaneously for restenosis and the sixth by bypass surgery. No adverse effects were attributable to everolimus or the polymer coating of the stents.

Table 4. Hierarchical major adverse cardiac events at 180 days in per-treatment population*.

| Event | Everolimus-stent n=26 | % | Bare-stent n=28 | % |
|------------------------------|--------------------------|-----|--------------------|------|
| Cardiac death | 0 | 0 | 0 | 0 |
| Myocardial infarction | | | | |
| Q-wave | 1† | 3.8 | 0 | 0 |
| Non-Q-wave | 0 | 0 | 0 | 0 |
| Reintervention | | | | |
| Clinically driven TLR-CABG | 0 | 0 | 1 | 3.6 |
| Clinically driven TLR-PCI | 1§ | 3.8 | 5 | 17.9 |
| Clinically driven TVR-CABG | 0 | 0 | 0 | 0 |
| Clinically driven TVR-PCI | 0 | 0 | 0 | 0 |
| Target vessel failure | 2 | 7.7 | 6 | 21.4 |
| Major adverse cardiac events | 2 | 7.7 | 6 | 21.4 |

* One patient in each group withdrew consent after treatment

** No statistical significance was detected between groups for all endpoints tested.

† Q-wave MI due to thrombosis of a non-study stent in a non-target vessel.

§ Clinically driven TLR for persistent dissection proximal to the stent 3 weeks after the index procedure.

Discussion

The main finding of this randomized first-in-man study is that an everolimus-eluting stent coated with a durable polymer was associated with an in-stent angiographic late loss of 0.10 mm, significantly less than the corresponding bare cobalt chromium metal stent of 0.87 mm, which satisfied the primary endpoint of this trial and confirmed the efficacy of this system. Correspondingly, in-segment late loss was also significantly less in the everolimus-stent group. Currently, two different drug-eluting systems (sirolimus and paclitaxel) are available. Although no published scientific comparative data is to date available, it appears that, from historical randomized trials, a difference of approximately 0.2 mm in-stent late loss exists between sirolimus and paclitaxel. Even if the impact of restenosis and MACE is currently unknown, some slight difference in restenosis rates and MACE can be expected. New devices should at least equal the incumbents in performance. This performance may be judged on late

loss, restenosis rate and / or the need for reintervention. With an in-stent late loss ranging from zero to 0.2 mm, it has been difficult to find a compound with the same efficacy, without resorting to the -limus family (Figure 5). With the sirolimus molecule being rather large and complex, it is therefore not surprising that major pharmaceutical companies have thoroughly explored its numerous analogues in order to develop a suitable competitor to sirolimus. The drug used in this study, everolimus differs from sirolimus by a substitution of a hydrogen radical/side-branch with a methyl sidechain.

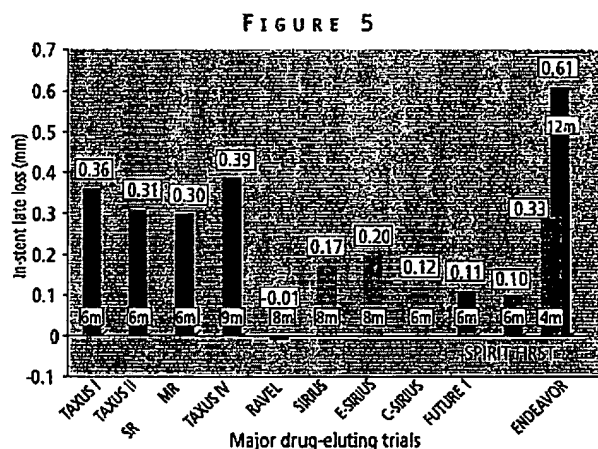


Fig. 5: Comparison of in-stent late loss from drug-eluting trials.

The reason for developing new compounds is to improve on the side effects of the existing compounds such as delayed healing with re-endothelialization and fibrin¹¹, early¹² and late stent thrombosis¹³. The success of the device lies in its three components - the drug, the polymer properties and the stent. The use of a sirolimus analogue is not in itself a guarantee of success since some of them have intrinsically, a potency in inhibition of up to 100 times less (e.g. tacrolimus), and some other analogues with equal *in vitro* inhibitory effects nevertheless fail to equally inhibit neointimal growth *in vivo*, because their duration of elution was suspected to be too short. However it has already been demonstrated that everolimus in clinical trials using a bioerodible polymer with a slower elution profile than sirolimus is effective in reducing late loss to below 0.2 mm⁴. Therefore the remaining challenge was to establish whether everolimus eluted from a durable polymer was also efficient and is addressed in this report.

Although the 6-month results are promising, one year angiographic and IVUS follow-up results are awaited to confirm the long-term results of this device in light of recent findings regarding an increasing late loss seen with other devices over time.

At the time of the publication of RAVEL, it was argued that the restenosis rate of the bare stent was excessively high at 26%. Similarly, in the present trial the restenosis rate in the bare stent arm was 25.9%. Nevertheless, it must be emphasized that in both cases these restenosis rates correspond to the value predicted and derived from multivariate analyses including as determinant parameters vessel size, MLD post, incidence of LAD disease and diabetics. Of Inter-

est, the late loss of the bare stent groups in RAVEL and this study were similar, corresponding to their restenosis rates. This is at variance with the VISION registry, and publications on stent strut thickness, but may be explained by the mismatch in stent size and reference diameter. This study was powered for late loss and not for clinical events, and it was not surprising that the 3 fold reduction in events failed to be statistically significant. At the time of trial design, safety studies with overlapping eluting-stents in animal models had not been completed, requiring the use of bare stents for bailout. As a result of this confounder, these patients were *a priori* excluded from the per-treatment analysis. This study was however designed as a first in man trial with everolimus on an untested new durable polymer in combination with a cobalt chromium stent.

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Appendix

Sponsor: Guidant Corporation, Santa Clara, California, USA.

Principal Investigator: Patrick W. Serruys (The Netherlands).

Executive Committee: P.W. Serruys (Principal Investigator and Chairman, Rotterdam, The Netherlands); Gary Johnson (Vice President of Regulatory Affairs/Clinical Research, Guidant Corporation); Stan Fink (Director of Clinical Research USA, Guidant Corporation).

Data Safety Monitoring Board (DSMB) - J.G.P. Tijssen, Amsterdam, The Netherlands; F.W.A. Verheugt, Nijmegen, The Netherlands; W. Wijns, Aalst, Belgium.

Clinical Events Committee (CEC) - J. Vos, Amphia Ziekenhuis, Breda, The Netherlands; B.J.W.M. Rensing, Sint Antonius

Ziekenhuis, Nieuwegein, the Netherlands; C. Hanet, Clinique Universitaire de Saint-Luc, Brussels, Belgium.

Data management - Angiographic and IVUS core laboratories: Cardialysis BV, Rotterdam, The Netherlands; Data Coordination Centre and Site Monitoring: Guidant Europe, Diegem, Belgium.

The following investigators and institutions participated in the SPIRIT First trial:

Clinical sites: J.J. Plek, Academisch Medisch Centrum, Amsterdam, The Netherlands (18 patients); F.J. Neumann, Herzzentrum, Bad Krozingen, Germany (14 patients); P.W. Serruys, Thoraxcentrum, Erasmus Medical Centre, Rotterdam, The Netherlands (5 patients); M. Wiemer, HZ Herzzentrum, Bad Oeynhausen, Germany (5 patients); A. Zeiher, Uni. Klinikum Frankfurt, Frankfurt, Germany (4 patients); E. Grube, Heart Center Siegburg, Siegburg, Germany (4 patients); J. Haase, Red Cross Hospital, Frankfurt, Germany (4 patients); L. Thuesen, Skejby Sygehus, Aarhus, Denmark (4 patients); C. Hamm, Kerckhoff Klinik, Bad Nauheim, Germany (2 patients).

Table A2. Appendix: results of intra vascular ultra sound analysis as per 180-day progress report - Clinical investigation plan 02-350 The SPIRIT first clinical trial. Guidant Corporation, Data on file.

| | Everolimus (n = 17) | Bare (n = 15) | P-value |
|--|------------------------|------------------|---------|
| Vessel volume (mm ³) | 299 ± 87 | 284 ± 77 | 0.76 |
| Stent volume (mm ³) | 138 ± 30 | 139 ± 39 | 1.00 |
| In-stent neo-intimal volume (mm ³) | 11.2 ± 14.0 | 41.4 ± 20.1 | <0.001 |
| Luminal volume (mm ³) | 126 ± 35 | 98 ± 34 | 0.06 |
| In-stent volume obstruction (%) | 8.6 ± 10.7 | 29.0 ± 13.9 | <0.001 |

Table A1. Appendix: results of sub-segmental quantitative coronary angiographic analysis (Unmatched Pairs) as per 180-day progress report - Clinical investigation plan 02-350 The SPIRIT first clinical trial. Guidant Corporation, Data on file.

| | Proximal edge | | | In-stent | | | Distal edge | | | In-segment analysis | | |
|---------------------------------|---------------------------------------|---------------------------------|---------|---------------------------------------|---------------------------------|-----------|---------------------------------------|---------------------------------|---------|---------------------------------------|---------------------------------|---------|
| | Everolimus (Post N=27 Fup N=23) | Bare (Post N=29 Fup N=26) | P-value | Everolimus (Post N=27 Fup N=23) | Bare (Post N=29 Fup N=26) | P-value | Everolimus (Post N=27 Fup N=23) | Bare (Post N=29 Fup N=26) | P-value | Everolimus (Post N=27 Fup N=23) | Bare (Post N=29 Fup N=26) | P-value |
| Main lumen diameter (mm) | | | | | | | | | | | | |
| After procedure | 2.49 ± 0.44 | 2.57 ± 0.39 | 0.44* | 2.34 ± 0.26 | 2.42 ± 0.31 | 0.41* | 2.18 ± 0.44 | 2.25 ± 0.42 | 0.67* | 2.07 ± 0.37 | 2.14 ± 0.37 | 0.74* |
| At 6 months | 2.45 ± 0.46 | 2.19 ± 0.50 | 0.05* | 2.28 ± 0.33 | 1.58 ± 0.42 | <0.001* | 2.18 ± 0.38 | 1.99 ± 0.46 | 0.19* | 2.04 ± 0.40 | 1.53 ± 0.41 | <0.001* |
| Late loss (mm) | 0.10 ± 0.17 | 0.38 ± 0.38 | 0.01* | 0.10 ± 0.23 | 0.84 ± 0.36 | <0.001*** | 0.07 ± 0.20 | 0.26 ± 0.41 | 0.14* | 0.09 ± 0.20 | 0.60 ± 0.36 | <0.001* |
| Diameter stenosis (%) | | | | | | | | | | | | |
| After procedure | 10 ± 10 | 15 ± 9 | 0.13* | 12 ± 4 | 15 ± 6 | 0.02* | 17 ± 10 | 19 ± 9 | 0.39* | 21 ± 8 | 24 ± 8 | 0.14* |
| At 6 months | 12 ± 12 | 18 ± 17 | 0.21* | 16 ± 8 | 39 ± 14 | <0.001* | 16 ± 10 | 20 ± 14 | 0.67* | 22 ± 11 | 41 ± 14 | <0.001* |
| Binary restenosis rates | 4.3% | 3.8% | 1.00** | 0.0% | 26.9% | 0.01** | 0.0% | 7.7% | 0.49** | 4.3% | 34.6% | 0.01** |

* Two-sided Wilcoxon rank sum test ** Two-sided Fisher's Exact test *** One-sided t-test

One-year results of a durable polymer everolimus-eluting stent in *de novo* coronary narrowings (The SPIRIT FIRST Trial)

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Ms. Veldhof and Ms. Dorange are employees of Guidant Corporation. The other authors declare no conflict of interests.

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KEYWORDS

Coronary artery
disease; eluting stent;
everolimus;
randomized trial

Abstract

Aim: Short-term results of durable polymer everolimus-eluting stents have shown significant improvements in clinical and angiographic outcomes. This report presents the 1-year clinical and angiographic data from the SPIRIT FIRST Trial.

Methods and results: This first-in-man single blind multi-centre randomized controlled trial assessed the safety and efficacy of everolimus and a durable polymer on a cobalt chromium stent in patients with *de novo* native coronary artery lesions. Of the 60 patients enrolled, a total of 56 patients (27 everolimus arm and 29 bare stent arm) were qualified to per-treatment analyses at 1 year. Quantitative angiographic and intravascular ultrasound (IVUS) analyses were performed. Angiographic late loss, IVUS neointimal volume obstruction and major adverse cardiac events (MACE) at 1 year were assessed as the study endpoints. At 1 year, the in-stent late loss and diameter stenosis of patients were 0.24 mm and 18% in the everolimus arm (n=20), as compared with 0.84 mm and 37% in the bare stent arm (n=25, p < 0.001). Significantly less neointimal hyperplasia was observed in the everolimus arm compared to the bare stent arm (neointimal volume, 13±9 mm³ vs. 37±17 mm³, p < 0.001; volume obstruction, 10±7% vs. 28±12%, p < 0.001). The overall MACE rate was 15.4% in the everolimus arm and 21.4% in the bare stent arm.

Conclusion: The safety and efficacy of everolimus-eluting stent with a durable polymer observed at 6 months was sustained at 1 year.

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Introduction

To date percutaneous coronary intervention (PCI) using drug-eluting stents is considered the most secure treatment option for *de novo* single coronary artery disease. The two clinically available stents coated with an anti-proliferative drug, sirolimus or paclitaxel, have shown promising clinical and angiographic outcomes as proven in several randomized trials¹⁻³. Beside these two drugs, the efficacy of newly developed antiproliferative drugs has been clinically investigated⁴⁻⁹ and their potent effects in preventing restenosis have been reported⁵⁻⁹.

Everolimus is a powerful anti-proliferative agent and has shown effect in preventing rejection in kidney and heart transplantation¹⁰⁻¹². In the presence of everolimus, the growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1 is inhibited. The latter proteins are key proteins involved in the initiation of DNA synthesis. Since phosphorylation of both p70 S6 kinase and 4E-BP1 is under the control of FRAP (FKBP-12-rapamycin associated protein, also called mTOR, mammalian Target Of Rapamycin), this finding suggests that, like sirolimus, the everolimus-FKBP12 complex binds to and thus interferes with the function of FRAP.

The SPIRIT FIRST clinical trial represents the first evaluation of the everolimus-eluting stent which studied the potential benefits of the local application of everolimus in a durable polymer in combination with a stent with a thin strut design⁵. Compared to identical bare metal stents, everolimus-eluting stents have demonstrated effective suppression of neointimal growth at 6 months⁵. This paper presents the 1-year clinical and angiographic/intravascular ultrasound (IVUS) follow-up results from the experience with the durable polymer everolimus-eluting stent.

Methods

Study population

The SPIRIT FIRST clinical trial was a prospective, controlled, randomized, single-blinded, parallel 2-arm, multicentre clinical evaluation of a durable polymer everolimus-eluting stent (XIENCE™ V, Guidant, Santa Clara, CA, USA) in patients with *de novo* native coronary artery lesions. Patient eligibility criteria, device description and study procedure were previously reported, along with 6-month clinical, angiographic and IVUS analyses⁵. Briefly, study patients had single *de novo* stenoses of < 18 mm lesion length, coverable by 1 study stent, > 50% diameter stenosis, and vessel reference diameter 3.0 mm as assessed by on-line quantitative coronary angiography (QCA). Patients were ineligible if they had any of the followings: evolving myocardial infarction; stenosis of an unprotected left main coronary artery, an ostial location, or located within 2 mm of a bifurcation; a lesion with moderate to heavy calcification, or an angiographically visible thrombus; a left ventricular ejection fraction < 30%; were awaiting a heart transplant, or had a contraindication to aspirin, clopidogrel, heparin and any other drugs related to this study.

Follow-up and study endpoint

Clinical evaluation was scheduled at 1, 6, and 12 months with annual evaluation up to 5 years. Angiographic and IVUS imaging was obtained at baseline, 6- and 12-month follow-up.

The primary endpoint was in-stent late loss at 6 months. The major secondary endpoint was percent (%) in-stent volume obstruction at 6 months based on IVUS analysis. Other secondary endpoints included the followings: a) in-stent late loss at 1 year; b) in-segment late loss at 6 months and 1 year including proximal and distal evaluations; c) in-stent% volume obstruction at 1 year; d) in-stent and in-segment% diameter stenosis at 6 months and 1 year; e) in-stent and in-segment angiographic binary restenosis (ABR) at 6 months and 1 year; f) persisting incomplete apposition, late incomplete apposition, aneurysm formation, thrombus, persisting dissection at 6 months and 1 year; g) major adverse cardiac events (MACE) rate in-hospital and at 1, 6, 9 months and annually up to 5 years. MACE is comprised of death, myocardial infarction (MI), or clinically driven target lesion revascularization (TLR); g) acute device, procedural and clinical success. All deaths that could not be clearly attributed to another cause were considered a cardiac death. A non-Q-wave myocardial infarction was defined by an increase in the creatine kinase level to more than twice the upper limit of the normal range, accompanied by an increased level of creatine kinase MB, in the absence of new Q waves on the surface electrocardiogram.

Quantitative Coronary Angiography evaluation

QCA was performed by means of the CAAS II analysis system (Pie Medical B.V., Maastricht, The Netherlands). In each patient, the stented segment and the peri-stent segments (defined by a length of 5 mm proximal and distal to the stent edge) were analyzed. The following QCA parameters were computed: minimal luminal diameter (MLD), reference diameter, and% diameter stenosis. ABR was defined in every segment as diameter stenosis >50% at follow-up. Late loss was defined as the difference between MLD at post-procedure and MLD at follow-up.

Intravascular Ultrasound Analysis

Post-procedure and follow-up stented vessel segments were examined with mechanical or phased-array IVUS using automated pull-back at 0.5 mm per second. A coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was also examined. A computer-based contour detection program (Curad B.V., Wijk bij Duurstede, The Netherlands) was used for automated 3-D reconstruction of the stented and the peri-stent segments. The lumen, stent boundaries and external elastic membrane were detected using a minimum cost algorithm. The stent volume (SV) and lumen volume (LV) were calculated according to Simpson's rule. The in-stent neointimal volume was calculated as "SV-LV". The % obstruction of the stent volume was calculated as in-stent neointimal volume/stent volume $\times 100$. Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated *in vitro* and *in vivo*¹³.

Statistical analysis

The primary endpoint and all trial endpoints were analyzed on the per-treatment evaluable population. Acute success was analyzed on the safety population. The per-treatment evaluable population consisted of patients who had no bailout and no major protocol deviations. The data for each patient were reviewed in a blinded

manner to determine whether the patient should be included in this analysis population. Analyses based on the per-treatment evaluable population were as "treated". Patients were included in the treatment arm corresponding to the study stent actually received.

The overall sample size calculation for this trial was determined based on the primary endpoint of in-stent late loss at 6 months and on the following assumptions: a single comparison of active to control; one-tailed t-test, unequal and unknown variances in the 2 groups being compared; $\alpha = 0.05$; true mean difference between the control group and the treatment group is 0.48 mm. This assumption was made based on the results of VISION Registry (mean late loss = 0.83 mm)¹⁴, SIRIUS trial (mean late loss = 0.17 mm)² and TAXUS IV trial (mean late loss = 0.39 mm)¹⁵. Assuming the true mean late loss for the treatment group was 0.35 mm, the difference between the control group and treatment group is calculated as: 0.83 mm - 0.35 mm = 0.48 mm. The standard deviation was assumed to be 0.56 mm in the control group and 0.38 mm in the treatment group (based on the results of VISION Registry study and SIRIUS trial with standard deviation for DES adjusted downward from 0.44 mm to 0.38 mm to take into account of 6-month angiography as opposed to 8-month angiography); approximately 20% rate of lost to follow-up or dropout; approximately 10% of patients with bailout stents; given the above assumptions, enrolling 30 patients per arm (analysis of 22 evaluable patients per arm) would have provided 95% power for comparison. Although the trial was not powered based on the major secondary endpoint, percent volume obstruction at 180 days, enrolling 30 patients per arm (analysis of 22 patients per arm) provides more than 96% power. Binary variables were compared using Fisher's exact test. For continuous variables, means and standard deviations were calculated and groups compared using the Wilcoxon's rank sum test. Time-to-event variables were compared with Kaplan-Meier analysis and the log rank statistic.

Results

A total of 60 study patients were randomized and consecutively enrolled at 9 investigational sites between December 2003 and April 2004. The safety population is composed of these 60 patients. Of the 60 patients, 3 were excluded from the per-treatment population (1 from the everolimus arm and 2 from the bare stent arm) because of bailout stenting (2) and major protocol deviation (1 patient on a heart transplant waiting list from bare stent arm). Hence the per-treatment population includes 56 patients (27 everolimus arm and 29 control) as illustrated in the trial profile (Figure 1). The control arm and the everolimus arm shared similar demographic characteristics except for patients with hypertension which was significantly higher in the everolimus group than in control (Table 1). Procedural characteristics were explained previously⁵.

One-year quantitative coronary angiographic analysis (Table 2)

Nine patients did not have qualifying follow-up angiogram up to 1 year for the following reasons: a) patients withdrew from the clinical trial after the 30-day follow-up visit (1 patient in the everolimus

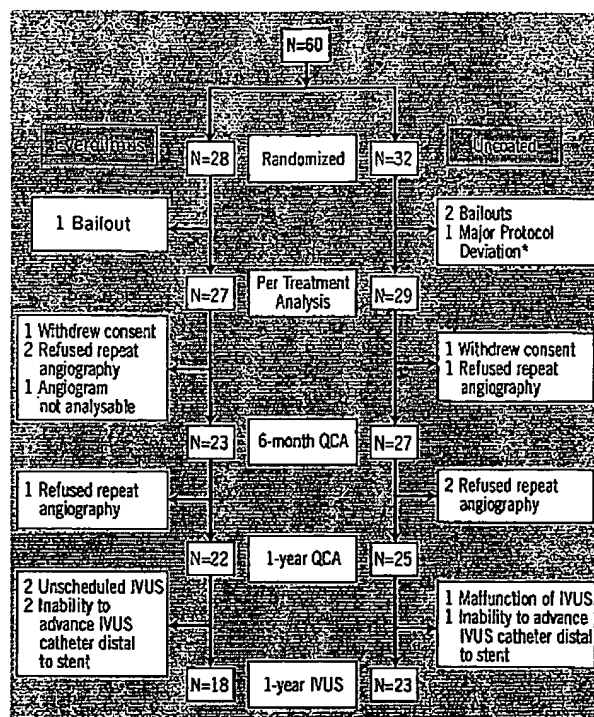


Figure 1. Flowchart of patients. QCA, quantitative coronary angiography; IVUS, intravascular ultrasound.

Table 1. Baseline characteristics of the per-treatment patient population and of each treatment group.*

| | Everolimus Stent (n=27) | Uncoated Stent (n=29) | All Patients (n=56) |
|---|----------------------------|--------------------------|------------------------|
| Age(yrs) | 64±10 | 61±9 | 63±9 |
| Male gender (%) | 70 | 76 | 73 |
| Current smokers (%) | 28 | 31 | 30 |
| Diabetes (%) | 11 | 10 | 11 |
| Hypertension requiring Medication (%) | 70 | 41 | 55 |
| Hypertlipidemia requiring Medication (%) | 70 | 76 | 73 |
| Prior intervention (%) | 19 | 7 | 13 |
| Prior MI (%) | 24 | 14 | 19 |
| Stable angina (%) | 78 | 79 | 79 |
| Unstable angina (%) | 19 | 14 | 16 |
| Target vessel (%) | | | |
| Left Anterior Descending | 48 | 45 | 46 |
| Left Circumflex | 22 | 21 | 21 |
| RCA | 30 | 34 | 32 |
| AHA / ACC# Lesion class (%) | | | |
| A | 0 | 10 | 5 |
| B1 | 41 | 28 | 34 |
| B2 | 59 | 62 | 61 |
| C | 0 | 0 | 0 |
| Reference vessel diameter (mm±SD) | 2.61±0.40 | 2.71±0.28 | 2.66±0.34 |
| Lesion length (mm±SD) | 10.1±2.6 | 10.9±3.3 | 10.5±3.0 |

* There were no significant differences between the treatment groups except for Hypertension Requiring Medication (P=0.04)

AHA / ACC = American Heart Association / American College of Cardiology.

Table 2. Results of sub-segmental quantitative coronary angiographic analysis (Serial analysis)

| | Proximal Edge | | | In-Stent | | | Distal Edge | | | In-segment Analysis | | |
|--------------------------------|-------------------------------|-----------------------------|---------|-------------------------------|-----------------------------|---------|-------------------------------|-----------------------------|---------|-------------------------------|-----------------------------|---------|
| | Everolimus-Stent (n = 20*) | Uncoated Stent (n = 25*) | P-value | Everolimus-Stent (n = 20*) | Uncoated Stent (n = 25*) | P-value | Everolimus-Stent (n = 20*) | Uncoated Stent (n = 25*) | P-value | Everolimus-Stent (n = 20*) | Uncoated Stent (n = 25*) | P-value |
| Reference vessel diameter (mm) | | | | | | | | | | | | |
| After procedure | 2.81±0.36 | 2.98±0.33 | 0.27 | 2.74±0.29 | 2.80±0.32 | 0.61 | 2.70±0.31 | 2.71±0.32 | 0.95 | 2.69±0.33 | 2.74±0.34 | 0.81 |
| At 6 months | 2.79±0.34 | 2.64±0.43 | 0.10 | 2.74±0.31 | 2.57±0.39 | 0.12 | 2.66±0.37 | 2.44±0.38 | 0.06 | 2.65±0.36 | 2.58±0.38 | 0.50 |
| At 1 year | 2.75±0.34 | 2.64±0.39 | 0.29 | 2.65±0.32 | 2.52±0.38 | 0.22 | 2.59±0.39 | 2.40±0.39 | 0.12 | 2.59±0.37 | 2.53±0.38 | 0.62 |
| Minimal luminal diameter (mm) | | | | | | | | | | | | |
| After procedure | 2.56±0.44 | 2.60±0.43 | 0.93 | 2.40±0.25 | 2.42±0.26 | 0.91 | 2.29±0.38 | 2.20±0.45 | 0.54 | 2.15±0.32 | 2.11±0.37 | 0.56 |
| At 6 months | 2.47±0.49 | 2.15±0.51 | 0.04 | 2.28±0.33 | 1.53±0.40 | < 0.001 | 2.23±0.32 | 1.99±0.46 | 0.08 | 2.07±0.38 | 1.49±0.39 | < 0.001 |
| At 1 year | 2.44±0.47 | 2.12±0.48 | 0.03 | 2.16±0.37 | 1.58±0.44 | < 0.001 | 2.26±0.38 | 1.96±0.43 | 0.05 | 2.01±0.41 | 1.52±0.42 | < 0.001 |
| Late loss (mm) | | | | | | | | | | | | |
| At 6 months | 0.09±0.19 | 0.45±0.42 | <0.01 | 0.12±0.22 | 0.89±0.39 | < 0.001 | 0.06±0.21 | 0.21±0.41 | 0.10 | 0.08±0.20 | 0.62±0.39 | < 0.001 |
| At 1 year | 0.12±0.25 | 0.48±0.39 | < 0.001 | 0.24±0.27 | 0.84±0.45 | < 0.001 | 0.03±0.25 | 0.25±0.42 | 0.04 | 0.14±0.24 | 0.59±0.42 | < 0.001 |
| Diameter stenosis (%DS) | | | | | | | | | | | | |
| After procedure | 9±11 | 13±9 | 0.53 | 12±6 | 13±7 | 0.36 | 15±10 | 19±11 | 0.22 | 20±6 | 23±9 | 0.18 |
| At 6 months | 12±14 | 18±18 | 0.17 | 17±7 | 41±14 | < 0.001 | 16±8 | 19±14 | 0.95 | 22±11 | 42±13 | < 0.001 |
| At 1 year | 11±13 | 19±15 | 0.12 | 18±13 | 37±17 | < 0.001 | 13±8 | 18±14 | 0.24 | 22±15 | 40±16 | < 0.001 |

*Patients who underwent angiography at 6 months as well as 1 year.

arm and 1 in the control arm); b) patients refused (3 in the everolimus arm and 3 in the control arm); c) angiogram was not analyzable (1 in the everolimus arm). Serial angiographic follow-up data, which is reported in this paper, were available in 80.4% (45/56) of the per-treatment population, with 74.1% (20/27) in the everolimus arm and 86.2% (25/29) in the control arm (Table 2). The follow-up in-stent MLD was significantly larger in the everolimus arm than in the control arm and the preservation of MLD between 6 months and 1 year was observed (2.28±0.33 mm at 6 months; 2.16±0.37 mm at 1 year). The mean in-stent late loss and % diameter stenosis were 0.24 mm and 18%, respectively, in the everolimus-stent group, as compared with 0.84 mm and 37%, respectively, in the control arm ($p < 0.001$ for each comparison). Figure 2 shows the cumulative frequency of in-stent late loss immediately after the index procedure at 6 months and 1 year in each

treatment group. The late luminal loss at both the proximal and the distal edges of the stent was less in the everolimus-stent group than in the control arm ($p < 0.001$ for proximal and $p = 0.04$ for distal). The in-segment late loss was significantly less in the everolimus arm than in the bare stent arm ($p < 0.001$).

One-year intravascular ultrasound evaluation (Table 3)

In this 1-year report, data in patients who underwent IVUS at 6 months as well as 1 year were presented to identify the volumetric change in serial IVUS examination. Forty-one patients (18 in the everolimus arm; 23 in the control arm) out of 47 patients with 1-year angiography underwent a 1-year IVUS examination. In the remaining

Table 3. Serial IVUS measurements at 1 year follow-up

| | | Everolimus-Stent (n = 16*) | Uncoated Stent (n = 25*) | P-value |
|---|----------|-------------------------------|-----------------------------|---------|
| Vessel volume (mm ³) | 6 months | 296±90 | 291±74 | 0.89 |
| | 1 year | 286±80 | 290±72 | 0.82 |
| Stent volume (mm ³) | 6 months | 137±31 | 138±31 | 0.94 |
| | 1 year | 133±27 | 137±32 | 0.79 |
| In-stent neo-intima volume (mm ³) | 6 months | 9±12 | 39±20 | < 0.001 |
| | 1 year | 13±9 | 37±17 | < 0.001 |
| Luminal volume (mm ³) | 6 months | 128±34 | 98±29 | 0.03 |
| | 1 year | 120±30 | 100±28 | 0.15 |
| In-stent volume obstruction (%)# | 6 months | 7±9 | 29±14 | < 0.001 |
| | 1 year | 10±7 | 28±12 | < 0.001 |

* Patients who underwent IVUS at 6 months as well as 1 year.

In-stent volume obstruction = 100* (In-stent neo-intima volume / Stent volume)

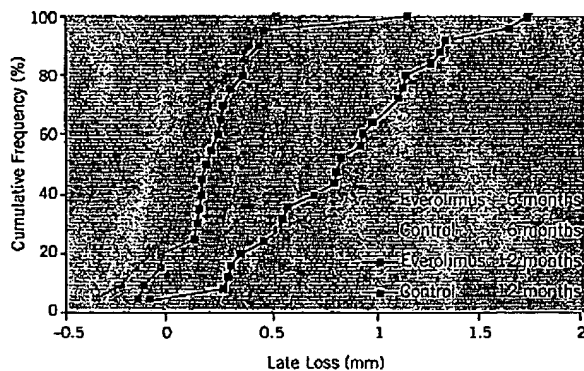


Figure 2. Cumulative frequency of late loss (in-stent) immediately after stenting.

6 patients, IVUS was not available: 2 were not properly scheduled for IVUS, 2 inability to advance IVUS catheter distal to stent in the everolimus arm; 1 malfunction of IVUS, 1 inability to advance the IVUS catheter distal to the stent in the control arm. Of the 41 patients, 37 patients (16 in the everolimus arm; 21 in the control arm) had serial IVUS data. Everolimus-eluting stent was associated with a significantly reduced degree of in-stent neointimal hyperplasia as well as in-stent% volume obstruction compared to the bare metal stent ($13 \pm 9 \text{ mm}^3$ vs. $37 \pm 17 \text{ mm}^3$, $p < 0.001$; $10 \pm 7\%$ vs. $28 \pm 12\%$, $p < 0.001$), reaching a 64% reduction of the in-stent volume obstruction (Table 3). There was no late acquired or persisting stent malapposition observed either at 6 months or at 1 year.

Major adverse events and clinical outcomes

Table 4 provides results of MACE and target vessel failure for the time points of 1 year. Since the six months follow-up the 1-year results for the everolimus arm included 1 non-Q wave MI due to a spasm during the follow-up IVUS procedure and 2 additional TLRs by PCI. One of these patients had a delayed bailout (TLR) using a non-study drug eluting stent 21 days after the baseline procedure due to a dissection. In the control arm, 1 additional TLR by PCI was observed, this being the patient's 3rd TLR since the index procedure. The hierarchical MACE rate at 1 year was 15.4% for the everolimus arm and 21.4% for the bare stent arm ($p=0.59$). The MACE rate for the everolimus group increased from 7.7% (2/26) at 6 months to 15.4% (4/26) at 1 year. Three of the 4 overall MACE events in the everolimus group were non-study-device related events. One Q-wave MI was in a non-target vessel, one TLR was due to dissection during the procedure, and one non-Q-wave MI occurred during follow-up IVUS procedure. Total non-hierarchical clinically-driven TLR rates at 1 year were 7.7% in the everolimus arm and 21.4% in the control arm. No adverse effects related to everolimus or the durable polymer were noted. Kaplan-Meier survival estimates were performed for overall MACE (Figure 3). There was no stent thrombosis observed in both arms out to the 1-year time period.

Table 4. Hierarchical Major Adverse Cardiac Events at 1 year in Per-Treatment Population

| Event | Everolimus Stent | | Uncoated Stent | |
|------------------------------|------------------|------|----------------|------|
| | n=26 | % | n=28 | % |
| Cardiac death | 0 | 0 | 0 | 0 |
| Myocardial infarction | 2 | 7.6 | 0 | 0 |
| Q-wave | 1 | 3.8 | 0 | 0 |
| Non-Q-wave | 1 | 3.8 | 0 | 0 |
| Reintervention | | | | |
| Clinically driven TLR-CABG | 0 | 0 | 1 | 3.6 |
| Clinically driven TLR-PCI | 2 | 7.7 | 5 | 17.9 |
| Clinically driven TVR-CABG | 0 | 0 | 0 | 0 |
| Clinically driven TVR-PCI | 0 | 0 | 0 | 0 |
| Target vessel failure | 4 | 15.4 | 6 | 21.4 |
| Major adverse cardiac events | 4 | 15.4 | 6 | 21.4 |

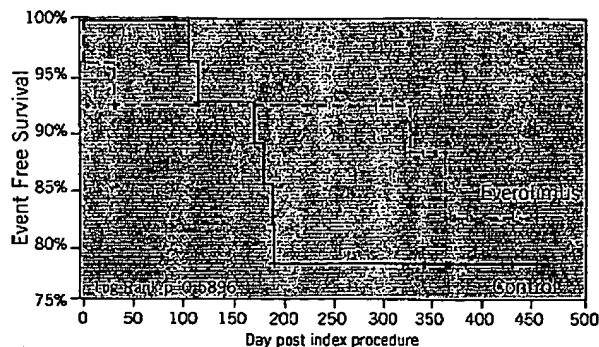


Figure 3. Kaplan-Meier survival curve: MACE. Since the 6-month time point, 1 non-Q wave MI due to a dissection during the follow-up IVUS procedure and 1 clinically-driven additional target lesion revascularization by PCI were observed in everolimus arm. In the control arm, 1 clinically-driven additional target lesion revascularization by PCI was performed.

Discussion

One-year clinical and angiographic follow-up from this trial demonstrates that the polymer-controlled release of everolimus from a coronary stent is safe and effective, with no late adverse effects. The superiority in efficacy, as measured by in-stent late loss, of everolimus-eluting stent as compared to bare stent was sustained at 1 year (71% reduction in late loss). The everolimus arm also maintained its superiority to the bare metal arm in the major secondary IVUS endpoint, % volume obstruction, at 1 year (64% reduction). In addition, the everolimus arm also continued to show significantly lower neointimal volume than the bare stent arm at 1 year (65% reduction).

The current strategy of local drug delivery using sirolimus and paclitaxel is the most promising approach to prevent restenosis, but, at the same time, the strategy has the potential liability for impairing endothelial recovery. Developing new compounds may improve on the potential side effects of the current drug-eluting stents, such as delayed healing with re-endothelialization¹⁶ and fibrin¹⁷, early¹⁸ and late stent thrombosis¹⁹. In this trial, neither stent thrombosis nor other adverse effects related to the drug/durable polymer was observed out to the 1-year time point. On the other hand, an *in vitro* study has shown that sirolimus enhances tissue factor in human endothelial cell²⁰. Effect of everolimus on endothelial cell and its similarity or difference compared to sirolimus will have to be investigated. The significant differences between sirolimus- and paclitaxel-eluting stents have recently been reported to likely exist with regard to angiographic as well as clinical outcomes^{21,22}. "New comers" following these 2 pioneers could be competitors if they can, at least, demonstrate performance as effective as these 2 drug-eluting stents. Studies have suggested that angiographic assessment of late loss is associated with an increased restenosis rate^{23,24} as well as a higher risk of TLR²⁵. However, it still remains to be determined how to interpret the significance of the slight increase in late loss from 6 months (0.12 mm) to 1 year (0.24 mm) observed in this study stent. Moreover, delayed neointimal growth beyond the first 6 to 9 months has been reported in serial IVUS analyses in some trials

as documented in everolimus-eluting stent (in-stent volume obstruction, 7% at 6 months to 10% at 1 year), which may raise a concern about potential late catch-up phenomenon of DES²⁶. Recent head-to-head comparative studies between sirolimus- and paclitaxel-eluting stent are still limited to short-term results^{21,22,25,27-30}. Beneficial short-term outcomes do not necessarily translate in long-term efficacy. For example, late catch-up phenomenon has been experienced in vascular brachytherapy³¹. In this respect, the follow-up period of 1 year still seems relatively short to assess the durable safety and efficacy of one drug-eluting stent. However, neither sirolimus- nor paclitaxel-eluting stent have been associated with gradually increasing MACE over the years^{32,33}. Therefore, we could expect a similar lasting treatment effect of this new eluting stent.

Study limitation

This study with a small patient population provided only safety and efficacy data. Two larger single-blind, randomized controlled studies (The SPIRIT II and SPIRIT III) further evaluating this study stent compared to the paclitaxel-eluting stent for the treatment of coronary artery disease are under way.

Conclusions

At 1 year, this trial demonstrated that the treatment effect observed at 6 months was sustained at 1 year for everolimus-eluting stent. The in-stent and in-segment late loss in the everolimus arm was reduced by 71% and 78% compared to those in the bare metal arm, respectively. These observations were consistent with IVUS measurements. The 1-year results showed a reduction of neointimal volume by 65% as compared to bare metal stent. A small increase in % volume obstruction in event-free patients was observed from 6 to 12 months, but is considered clinically insignificant. Both the angiographic and IVUS measurements showed that the patency of the target vessel treated with everolimus-eluting stent was maintained at 1 year.

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